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Growing Research in Plant Technologies

Plant synthetic biology is an emerging field that combines engineering principles with plant biology to develop technologies for bioengineering plants. Plant bioengineers are responsible for the emergence of new technologies related to medical *Cannabis*.

Many jurisdictions in the U.S. and Canada allow the use of *Cannabis* or its derivatives for medical purposes. There is evidence supporting the effectiveness of medical-*Cannabis* treatment regimes, and sales of *Cannabis* in the U.S. are projected to reach $7 billion in 2016. So it comes as no surprise to see new and established companies increasing their investment in innovations related to *Cannabis*-based technologies.

Cannabis is a genus of flowering plant that includes three species — *sativa*, *indica*, and *ruderalis* — with different potential medical benefits. Some of the active components of *Cannabis* include terpenes, phenols (in particular stilbenoids and lignans), and the cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD). Although THC has typically received the spotlight in medical research, the medical usefulness of CBD has been more-intensely explored in recent years. Tests with patients who have medical disorders like cancer, multiple sclerosis, and chronic neuropathic pain have reported evidence supporting the efficacy of cannabinoids, but more clinical trials are needed to shed light on its application for other medical conditions.

Researchers in the U.S. who want to conduct clinical research using *Cannabis* must interact with three federal agencies. They must obtain *Cannabis* for research from the National Institute on Drug Abuse (NIDA) within the National Institutes of Health (NIH). They must submit an investigational new drug (IND) application and their research protocol to the Food and Drug Administration (FDA). And they must obtain an investigator registration and site licensure from the Drug Enforcement Administration (DEA).

Obtaining the *Cannabis* is only the first step. Extracting and separating cannabinoids from the plant in large yields and at high purities is challenging. Easier access to *Cannabis'* unique constituents would enable more testing of their separate effects. One way to achieve this is by producing synthetic cannabinoids, which are a chemically diverse group of compounds that function similarly to THC. Although there are no FDA-approved drugs derived from botanical *Cannabis*, the FDA has approved a drug that contains a synthetic version of a substance present in *Cannabis*. Another FDA-approved drug contains a synthetic substance that acts similarly to compounds in *Cannabis* but is not actually present in the plant. Clinical trials with synthetic cannabinoids have reported various, and sometimes opposite, effects, so additional studies are necessary.

Another way for scientists to access the active molecules in *Cannabis* is by producing THC and CBD using bioengineered yeast. Biochemists at the Univ. of Dortmund in Germany have engineered a yeast strain expressing the Δ9-tetrahydrocannabinolic acid synthase (THCAS) from *Cannabis sativa (1)*. THCAS is responsible for the bioconversion of cannabigerolic acid to THCA (a THC precursor). The same researchers also claim to have unpublished data that show the successful bioengineering of a yeast strain that makes CBD. Although further research is required, these engineered yeast strains may enable synthesized pharmaceutical THCA and CBD.

As the use of *Cannabis* grows, so do concerns about inconsistent and inaccurate dosages of *Cannabis* compounds. Entrepreneurs have formed numerous small companies across the U.S. and Canada to verify and certify the amount of active ingredients in *Cannabis* products to satisfy both authorities and consumers. Most *Cannabis* products are analyzed using high-performance liquid chromatography (HPLC). A major limitation of this method is that it is not suitable for analyzing diverse products, such as edibles and complex mixtures. New protocols and techniques for separating THC and other cannabinoids from complex mixtures are being proposed and tested by scientists and chemical engineers.

The resurgence of *Cannabis* is not only due to its phytochemical assets, but also because it is a rich source of cellulosic and woody fibers and a potential food source. Hemp is an industrial variety of the *Cannabis* plant that has extremely low concentrations of THC, CBD, and other cannabinoids. It is grown for its strong inner stem tissues, which are used to make bioplastics and materials similar to concrete. The hemp seeds can be consumed raw or pressed into an oil as a source of fatty acids and high-value proteins.

To learn more about *Cannabis* technologies, as well as other plant-based technologies, attend the International Conference on Plant Synthetic Biology and Bioengineering, Dec. 16–18, 2016, in Miami, FL, presented by the Society for Biological Engineering (SBE) (www.aiche.org/sbe). CEP

Literature Cited

1. **Zirpel B., *et al.,*** "Production of Δ9-tetrahydrocannabinolic Acid from Cannabigerolic Acid by Whole Cells of *Pichia (Komagataella) pastoris* Expressing Δ9-tetrahydrocannabinolic Acid Synthase from *Cannabis sativa L.*," *Biotechnology Letters*, **37** (9), pp. 1869–1875 (Sept. 2015).

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